



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,198	08/10/2001	James Arthur Hoffmann	X12383N	6700

25885 7590 08/16/2002

ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER

DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
----------	--------------

1647

DATE MAILED: 08/16/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/928,198

Applicant(s)

HOFFMANN ET AL.

Examiner

Regina M. DeBerry

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 92-103 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 92-103 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

Status of Application, Amendments and/or Claims

The amendment filed 05 June 2002 (Paper No. 8) has been entered in full.
Claims 92-103 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The objection to the specification as set forth at page 2 of the previous Office Action (06 March 2002, Paper No. 7) is *withdrawn* in view of the amendment (05 June 2002, Paper No. 8).

Claim Rejections - 35 USC § 103

Claims 92-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeMeere *et al.* (US Patent No. 5,384,132) in view of Buch-Rasmussen *et al.* (US Patent No. 5,945,187) and Bornstein *et al.* (US Patent No. 5,681,822). - The basis for this rejection is set forth at pages 3-4 of the previous Office Action (06 March 2002, Paper No. 7).

Applicant's arguments have been fully considered but not deemed persuasive for the following reasons.

Contrary to Applicant's assertion, the MPEP 2143 states (3) the prior art reference **(or references when combined)** must teach or suggest all the claim limitations. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

Art Unit: 1647

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant states that the DeMeere reference provides no teaching with respect to the stability of the reconstituted preparation. Instead, DeMeere exemplifies the stability of lyophilized formulations only, comprising FSH and various dicarboxylic acid salt stabilizers. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-lyophilized FSH) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims as cited in the instant application embrace all forms of human FSH. Furthermore, DeMeere states "the invention also includes a method of stabilizing an essentially pure gonadotropin, in lyophilized form, which method involves mixing the gonadotropin, in solution, with a sufficient amount of *a dicarboxylic acid salt to stabilize the protein* in the lyophilized form, **and then freeze-drying the resulting solution** to form

Art Unit: 1647

a stabilized lyophilisate of the gonadotropin" (column 1, line 66-column 2, lines 5).

Lyophilization is the process of isolating a solid substance from solution by freezing the solution and evaporating the ice under vacuum. Thus, the gonadotropin is in a solution with the stabilizing agent (the dicarboxylic acid) before the lyophilization process.

DeMeere also states that, "in order to prevent or slow down this degradation, attempts were made to freeze dry (lyophilize) the preparations. Lyophilization has only been partially successful however". DeMeere invention involves the use of dicarboxylic acid salt stabilizers. The DeMeere reference was used to cite that recombinant human FSH (FSH concentrations which overlap in the instant) can be stabilized with dicarboxylic acid salt in a pharmaceutically acceptable formulation.

Applicant states that the Bornstein reference teaches stability, measured only by solubility of a nucleoside in varying concentrations of benzyl alcohol. Contrary to Applicant's assertion, Bornstein teaches that "2-CdA has limited stability in simple saline solutions. Longer shelf-life is beneficial for extended storage at refrigerated or room temperature conditions"(column 1, lines 43-50). Bornstein states that "benzyl alcohol is known generally as a *preservative* in pharmaceutical formulations based on its antibacterial action and as a *solubilizing agent* for certain pharmaceutical compounds" (column 2, lines 18-24).

Applicant states that the Buch-Ramussen reference does not disclose or teach the stability of the protein stored in the polymeric container. Contrary to Applicants assertion, the polymeric container invention of Buch-Ramussen is not the reason why the reference was cited. The container just controls the loss of preservatives. Most

Art Unit: 1647

importantly, the reference teaches that insulin or growth hormones are normally provided with preservatives such as benzyl alcohol (column 1, lines 25-45). Applicant has stated that the stability of the non-covalently bonded heterodimer is not predictable based on the stability and/or solubility of a covalently bonded nucleoside or monomeric protein. However, insulin is made up of two chains. The amino-terminal peptide of mature insulin is called the B-chain and the carboxy-terminal peptide is called the A-chain. The chains are held together by two inter-chain disulfides. Applicant states that prior art teaches that preservative tend to denature or destabilize protein or induce aggregation. Applicant cites page 54, lines 26-30 in the instant specification. However, the specification states "preservatives" tend to denature or destabilize protein or induce aggregation. The specification does not teach that benzyl alcohol specifically denatures/destabilizes or induces aggregation of FSH, nor were references cited to demonstrate this. Therefore, there is no evidence that FSH would be expected to behave differently in benzyl alcohol.

Claims 96-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeMeere *et al.* (US Patent No. 5,384,132) in view of Buch-Rasmussen *et al.* (US Patent No. 5,945,187) and Bornstein *et al.* (US Patent No. 5,681,822) as applied to claims 92-95 and further in view of Carey *et al.* (US Patent No. 4,746,508). The basis for this rejection is set forth at pages 4-5 of the previous Office Action (06 March 2002, Paper No. 7).

Applicant's response to the rejection under 35 USC 103(a) regarding the disclosures of DeMeere, Buch-Rasmussen and Bornstein, the summary of Applicant's argument and the law relating to obviousness under 35 USC 103(a) were previously discussed. Applicant's arguments have been fully considered but are not found to persuasive for the reasons discussed above in the maintained rejection.

Applicant states that the Carey reference does not teach or suggest that the disclosed compositions are useful without the steroid adjuvants. Applicant states that Carey does not address or demonstrate any of the following: stability of the composition, with or without the steroid adjuvant, multi-use of the composition or use of the composition as a parenteral drug. Applicant states that Carey requires that the composition contain a steroid adjuvant. The instant applicant does not require the addition of a steroid adjuvant.

It is irrelevant whether Carey used a steroid adjuvant. The Carey reference was cited to demonstrate that sodium phosphate is commonly used in pharmaceutical preparations. Pharmaceutical compositions are kept at a certain pH. Sodium phosphate (cited in the instant claims and Carey reference) only serves as the buffer. See the background in the instant specification regarding phosphate buffers (page 17, lines 9-30).

Contrary to Applicant's assertion, the prior art references, when combined teach all the claim limitations. As was stated above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of

Art Unit: 1647

references. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



RMD
August 9, 2002



ELIZABETH KEMMERER
PRIMARY EXAMINER